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ABSTRACTS OF RECENT PHD THESES (2003)

BIOMIMETIC MODELLING OF BIOLOGICAL OXIDATIONS

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Oxidative processes catalysed by metalloporphyrins are gaining nowadays importance in the study of various biological systems. One of the main direction of the investigations with synthetic metalloporphyrin catalysts is the development of systems which are capable of reproducing oxidative processes mediated by hem proteins (such as cytochrome P450, lignin peroxydase, nitric oxide synthase (NOS), etc.). Another possible application is to develop systems containing metalloporphyrin catalysts, which could selectively oxidize organic compounds or detoxificate polluting agents at industrial level.

We proved the benefits of the application of pentafluoride iron porphyrin used in three fields: – in the insect selective cytochrome P450 catalyzed metabolism of carbamate insecticides, – to verify the natural decomposition path of insect selective cytochrome P450 inhibitors (metabolic pathways of lignin peroxydase), – in modelling the H_2O_2 dependent NOS catalyzed oxidation of the *N*-hydroxyguanidine based NO donors.

Degradation and the antioxidative effect of Na-, Zn-, Co-, Cu- and Mn- HA (hyaluronan) associates were studied. Our findings have revealed the protective effect of certain counter-ions against ROS (reactive oxygen species) induced HA degradation. We could also separate the antioxidative effect of certain counter-ions from that of the HA by examining the effect of the counter-ions in their free ionic forms. The result showed that metal ions with altering oxidative status (Co^{2+}, Cu^{2+}, Mn^{2+}) proved to be effective in themselves or their effect added to that of HA when HA was also effective. Moreover, the effect of Co-HA against O_2^- and that of Mn-HA against $ONOO^-$, as well as the synergic effect of Zn-HA associates where Zn^{2+} is of fixed oxidative status were attributed to the structure-stabilizing complex formed between certain counter-ions and HA.

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PREPARATION OF SOLID ACID CATALYSTS AND THEIR APPLICATION IN FRIEDEL-CRAFTS TYPE ACYLATION REACTIONS

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Nowadays, in the applied technologies those environment-friendly processes are preferred which involve the reduction or elimination of the by-product formation. Conventional Friedel-Crafts acylation produces high amount of non-regenerable, useless chemicals. Consequently, researches to find regenerable and efficient catalysts have a great importance. After catalyzing the reaction, the solid acids can be removed from the reaction mixture in a simple way, by a mechanic filtration for example. The aim of my research work was to find a new, heterogeneous catalytic way for the Friedel-Crafts acetylation of the benzo-15-crown-5 crown ether (B15C5) using solid acid catalysts.

Methods

The physical and chemical properties of the applied sulfated zirconia and clay catalysts have been studied by chemical analysis, thermal analysis, measuring the specific surface area, temperature programmed ammonia desorption and reflexion FT-IR spectroscopy. The chemical reactions were followed with HPLC chromatography.

New Scientific Results

1. According to my investigations there are significant differences between structure and properties of sulfated zirconia catalysts prepared by one-step and of those prepared by two-step method. Catalysts prepared by the two-step method: (i) contain only one sulfate species (corresponding to the DTG curves) which decomposes in a higher range of temperature; (ii) after calcination they do not contain strongly acidic hydroxyl groups which can be linked with sulfate groups; (iii) contain less strongly acidic disulfate groups than weakly acidic monosulfate groups. Catalysts prepared by the one-step method: (i) contain two sulfate species even before calcination; (ii) after calcination they contain in higher proportion the strongly acidic disulphate species; (iii) the acidity of their OH groups linked to Zr-atoms corresponds to that of the HX-zeolite.
2. Sulfated zirconia catalysts prepared by the two-step method show relatively lower activity either in the acylation of anisole by acetic anhydride or in that of benzo crown ether than the catalysts prepared by sol-gel methods. This experience corresponds well to the measured lower acidity of the former type catalysts than that of the latter one.

3. There are significant differences between the two sub-types of catalysts prepared by the one-step method: (i) If sulfuric acid is mixed first with water and then added to zirconium propoxide, the hydrolysis is not completed, there is always some residual organic material present in the gel. (ii) If sulfuric acid is dissolved in zirconium propoxide and after that water is added to the mixture, the resulted product has definitely higher specific surface area than the previous one, has a heterogeneous pore distribution and contains the highest number of acidic sites. H_2SO_4 is thus not only a source of sulfur but it plays an important role in the mechanism of the hydrolysis.
4. A method has been elaborated to the heterogeneous catalytic acylation of B15C5 with acetyl chloride. Although diffusion control is out of question, no relations were found between acidity and activity of the catalysts (namely K10 and its ion-exchanged derivatives). The best results could be achieved by Sn^{2+}-K10 and Fe^{3+}-K10 (these catalysts contain variable valency metals). This latter observation led us to propose, following literature analogies, a redox mechanism initiated by a radical attack.
5. For the acetylation of B15C5 a method with acetic anhydride has also been elaborated (without solvent). Best result could be achieved with Sn^{2+}-K10 catalyst (57% preparative yield). By studying the effect of the heat treatment of the ion-exchanged K10 catalysts one could conclude that the activity of such catalysts is determined by their Brønsted acidity.
6. In these two types of acetylation of crown ethers sulfated zirconia catalysts gave different results, however, the best yields could be obtained with catalysts prepared by sol-gel method (water added to the mixture of zirconium propoxide $+H_2SO_4$), independently of the used solvent. These catalysts applied in acetic anhydride gave almost the same performance as Sn^{2+}-K10 (in accordance with the Brønsted-acidity); on the other hand they gave poor results with acetyl chloride. This fact can be an indirect approval of the proposed redox mechanism initiated with a radical attack.

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INVESTIGATION OF BIOCATALYSTS AND BIOCATALYTIC PROCESSES AND THEIR SYNTHETIC APPLICATIONS

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The primary aim of my PhD research was to investigate the enzyme production of thermophilic filamentous fungi strains and to study the lipase/carboxylesterase activities which can be applied effectively as general biocatalyst in organic synthesis practice. Investigation of these enzyme products in common and novel biocatalytic processes was also a part of my research work.

45 thermophilic filamentous fungi (18 have not been identified yet) were cultivated in shaken flasks in two different media, and the supernatants were assayed for lipase/carboxylesterase activities using olive-oil, *p*-nitrophenyl palmitate and *p*-nitrophenyl butyrate as substrates. The 90 crude enzyme powders (acetone precipitated supernatants) were tested as biocatalysts in organic solvents.

25 strains of thermophilic filamentous fungi exhibiting high enzymatic activity were chosen for cultivation on two different solid state media and the lipase/hydrolase activities in the supernatant were evaluated. About 45 dried enzyme products were prepared by drying the fermentation matrix containing the fungi mycelium. These products proved to be inexpensive, easy-to-handle and reliable, therefore, their patenting has been taken into consideration.

Although hydrolases (lipases/esterases) were detected in numerous thermophilic fungi strains, only a few have been evaluated as synthetic biocatalyst yet. Therefore, we thought worthwhile to characterize the biocatalytic abilities of enzymes from thermophilic fungi by two typical enantioselective processes. Both enantiotopic selectivity (2-acyloxi-1,3-propanediols) and enantiomer selectivity (1-phenylethanol, glycerine-carbonate, *trans*-cycloalkane-1,2-diol monoacetates, 1-(benzofuran-2-il)ethanols, 1-(benztiazol-2-il)-ethanol) were assayed by desymmetrization with enzymatic acetylation using vinyl acetate.

The tested biocatalysts proved to be comparable to the commercially available enzymes with respect to the degree of enantiomer selectivity, whereas they exhibited a wider range of enantiotopic selectivity than the most common commercial enzymes.

According to the initial goals, several biocatalysts for general application have been produced. Among the enzyme preparations investigated in organic synthetic reactions, a number of biocatalysts have been found which catalyze processes at a rate and with selectivity similar to that of commercially available enzymes. In a few cases, the other enantiomer product was successfully recovered by our enzyme preparations. The most significant of our results was the production of an enzyme

preparation (BUTE-3b), which catalyzed several processes with even greater selectivity than the commercially available enzymes. The submission of a patent engaged in this enzyme preparation is being considered.

Publications:

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COMPARATIVE STUDY OF HUNGARIAN WHITE AND RED WINES ON THE BASIS OF FREE AMINO ACID AND BIOGENIC AMINE CONTENTS

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Wines are known to contain many biologically active compounds. In my research effects of wine-making technology, geographical origin (wine-making region), grape variety and year of vintage were investigated according to free amino acid and biogenic amine contents of Hungarian wines. Determination of free amino acids and biogenic amines was accomplished by ion-exchange chromatography.

The total content of free amino acids ranged from 267.18 mg/dm^3 to 3536.24 mg/dm^3 in white wines (on average 1094.57 mg/dm^3), and from 373.37 mg/dm^3 to 3145.68 mg/dm^3 in red wines (on average 1273.46 mg/dm^3). The dominant free amino acids were proline and arginine. Ratios of proline to arginine were successfully used to differentiate between white and red wines (1.98 in white wines, 14.38 in red wines).

The total content of biogenic amines varied from 0.44 mg/dm^3 to 28.56 mg/dm^3 in white wines (on average 4.76 mg/dm^3), and from 1.16 mg/dm^3 to 33.85 mg/dm^3 in red wines (on average 7.19 mg/dm^3). The main biogenic amines were putrescine and tyramine. Ratios of putrescine to tyramine were useful to distinguish white and red wines (0.48 in white wines, 2.44 in red wines).

Among chemometric techniques linear discriminant analysis (LDA) and principal component analysis (PCA) were applied to data. Good differentiation was achieved between various groups of wines. Wine-making technology had greater effect on classification of wines than geographical origin, grape variety and year of vintage.

Based on the results of chemometric analyses, free amino acid and biogenic amine contents seem to be useful to differentiate wines according to wine-making technology, geographical origin (wine-making region), grape variety and year of vintage, too.

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CHEMO- AND ENANTIOSELECTIVE HETEROGENEOUS CATALYTIC HYDROGENATION OF EXCYCLIC α, β-UNSATURATED KETONES

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My PhD work comprised the study of the chemo- and enantioselective hydrogenation of three exocyclic α, β-unsaturated ketones: (*E*)-2-benzylidene-1-indanone, (*E*)-2-benzylidene-1-tetralone, (*E*)-2-benzylidene-1-benzosuberone, which are similar in functional groups, but different in their conformational properties.

The model compounds contain beside the C = C double bond in α-position a carbonyl group, therefore they can take up three moles of hydrogen with the saturation of C = C and C = O and hydrogenolysis of the C-OH bond. The objective of my work was the chemoselective saturation of the C = C double bond accompanied by the enantioselectivity with respect to the formed asymmetric carbon.

The chemoselectivity depends on the catalyst, solvent and the reaction conditions. The enantioselectivity depends on the chiral additive, the model compounds, the catalyst, the solvent and the reaction conditions.

For the selective saturation of the C = C double bond different noble metals and supports in different solvents were studied. The Pd/C catalyst was the best from the point of view of both the selectivity and the reaction rate. The chemoselectivity was the highest in toluene (90%), among the achiral additives pyridine was the best in all solvents (except ethyl-acetate), affording 100% chemoselectivity.

The effect of (*S*)-proline and other amino acids together with sodium methylate was tested in various solvents. Acetonitrile seemed to be the most suitable solvent with sodium-methylate additive for all the three substrates, (*E*)-2-benzylidene-1-indanone, ee: 13.8%, (*E*)-2-benzylidene-1-tetralone, ee: 10%, (*E*)-2-benzylidene-1-benzosuberon, ee: 20.1%. The formation of the enantiomers in excess was evaluated with molecular modelling calculations counting on the formation of a covalent bond between the substrate and the chiral auxiliary.

The hydrogenation of the model compounds was studied in the presence of chiral modifiers, among others of cinchona alkaloids.

On the basis of precedent experiences the studies were focused on the most suitable catalysts, solvents and reaction conditions for the enantioselectivity beside complete chemoselectivity. The enantioselectivity with cinchonidine in case of the (*E*)-2-benzylidene-1-indanone in methanol over Pd black was 9.6%, for (*E*)-2-benzyilidene-1-tetralone in acetonitile over Pd/TiO_2 was 9.1% and for (*E*)-2-benzylidene-1-benzosuberone in toluene over Pd black was 53.7%.

The working mode of the chiral auxiliary (*S*)-proline was explained with molecular modelling, calculating the energetically most favourable conformation

of the transitional complex. Similarly the effect of cinchonidine was explained by the interaction of the modifier and the substrate and by the steric hindrance in this transitional associate.

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INTERFACIAL INTERACTIONS IN CARBON FIBER REINFORCED COMPOSITES: SURFACE CHEMISTRY AND ADHESION

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The research directed towards the determination of the role of interfacial interactions developing in carbon fiber reinforced composites as well as the attempts to modify them yielded numerous new results. We found that the conditions of electrolytic oxidation of carbon fibers significantly influence the type and number of functional groups formed on the surface. Type, concentration and potential of oxidation, all influence the composition of the surface. Close correlation was found between the number of certain functional groups formed on the surface during oxidation and interfacial adhesion. Interaction between the fiber and the matrix can be modified by the application of coupling agents. Experiments carried out with various coupling agents proved that numerous chemical reactions take place on the surface of the fiber. The structure and properties of the coupling agent layer forming on the surface considerably influence the strength of adhesion and the properties of the composites. The coupling agents often take part in complicated polymerization reactions on the surface of the fiber.

The structure of the polymer layer depends on the chemical composition of the coupling agent and on the conditions of surface treatment. The obtained results proved that neither a rigid, stiff nor a weak layer improves interfacial adhesion, both lead to composites with inferior properties. Besides interfacial interactions composite structure plays also an important role in the determination of properties in short carbon fiber reinforced composites. Fiber orientation and orientation distribution as well as fiber length and its distribution influence the properties of the composites. A skin-core structure develops during the injection molding of a product and fiber orientation differs considerably in the two layers. The thickness of the skin depends on composition and on processing conditions. We found that the stiffness, strength and impact resistance of the composite increases with fiber content at moderate and high concentrations, but a small amount of fiber decreases impact resistance, because fibers behave like weak sites in the composite, they initiate fracture.

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DEVELOPMENT AND APPLICATION OF ENZYME-LINKED IMMUNOSORBENT ASSAYS

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The target of my PhD work was to develop an ELISA system for the detection of plant hormones and the herbicid trifluralin.

a. I developed an ELISA system for immunoanalytical detection of cytokinin hormones (N^6-(2-isopentenyl)-adenosine (IPA) and *trans*-zeatin riboside (ZR)).
   I coupled the two target hormones (ZR, IPA) to carrier proteins (BSA, OVA) and verified the efficiency of conjugation with SDS-PAGE.
   Using antisera against KLH-conjugates I developed a quick ELISA system (as a result of experiments with the incubation time) to analyse two types of cytokinin hormones. The IC_{50}values under optimized system parameters in the ZR and IPA ELISA systems are 19 ng/ml and 18 ng/ml, respectively. I optimized the systems for their main assay parameters (the effect of pH and solvent, incubation and preincubation time). I examined the pH (systems can tolerate values from 4.6 to 9.2), water miscible organic solvent (systems can tolerate methanol and ethanol content up to 8 V/V%, and acetonitril, aceton, DMF and DMSO content up to 2 V/V %) and the specificity for target hormones. I changed the peroxidase tracer enzyme to phosphatase to eliminate the matrix effect in plants, and verify that systems are suitable to measure the cytokinin concentration of plant samples.
b. I developed an ELISA system for immunoanalytical detection of the herbicide trifluralin.
   I coupled haptenic derivatives of the target analyte trifluralin to BSA and KLH proteins using different hapten/protein ratios. With UV and mass spectroscopy (MALDI-ToF) I verified that the hapten density in the conjugates is near the calculated values (1.02, 0.16 and 0.10 μmol hapten/mg protein, respectively).
   Using the antisera against the KLH-conjugate, a sensitive ELISA system (LOD: 0.85 ng/ml) was developed to determine trifluralin concentration in the low ppb range. I optimized the system for its main assay parameters (the effect of pH and organic solvents), and I checked the specificity for the target analyte. The advantage of the optimized system is its high specificity to trifluralin among dinitroaniline herbicides. The system can tolerate the pH in a wide range (4.6 9.4), the methanol content up to 5 V/V%, and the ethanol, acetonitrile, acetone, DMSO and DMF content up to 2 V/V%.

I validated the system in the trifluralin concentration range of 1–10 ng/ml using SPME/GC-MS. I studied the applicability of the method to the determination of trifluralin concentration in different surface water and vegetable juice samples. The results of these experiments show that the system is applicable to measure trifluralin concentration beside MRL level in the tested vegetable juices, in particular in the carrot juice.

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DEVELOPMENT AND APPLICATION OF ENZYME-LINKED IMMUNOSORBENT ASSAYS FOR PESTICIDE ACTIVE INGREDIENTS FENOXYCARB AND ATRAZINE

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Research during my PhD work includes two directions: development of *de novo* enzyme-linked immunosorbent assay (ELISA) systems, and application of ELISA systems, available from commercial or other resources, in various surveys.

(A) I developed a *de novo* ELISA system for immunoanalytical detection of the insect growth regulator fenoxycarb.

I coupled a haptenic derivative of fenoxycarb to carrier proteins. To verify coupling efficiency in conjugation of the aniline type haptens, I prepared model azo-compounds, and verified that hapten coupling strongly depends on the type of the carrier protein. I calculated the hapten/10 kDa protein ratios for carrier proteins (BSA, CONA, KLH and OVA), and these values were between 0.8 and 4.2, with the highest levels in the BSA- and CONA-conjugates.

I characterized the antisera against fenoxycarb immunogens in immobilized antigen-based ELISA systems. Serum titers in the developed ELISA systems were between 200 and 8000, and the inhibition mid-point (IC_{50}) with fenoxycarb in the optimized ELISA system was 2.7 ± 1.6 ng/ml and 1.1 ± 0.6 ng/ml with various conjugates.

I studied the cross-reactivity of 42 possible co-contaminants, and found the ELISA system specific for fenoxycarb. I optimized the ELISA system for its main assay parameters. The assay works the best at $pH = 7.4$, in a buffer containing 0.5% (v/v) methanol, using gelatin from bovine skin as a blocking reagent. I evaluated the applicability of the ELISA for environmental and biological samples. Thus, the system is applicable in water samples (tap water, water from the river Danube), while the analysis of soil samples requires sample clean-up. I used the optimized ELISA system for insect hemolymph, animal urine, and fish liver samples, where I detected increasing fenoxycarb content in the liver of treated animals dependent of the application dose. Using water and fruit drink samples, I compared the optimized ELISA system with an instrumental analytical (GC-MS) method.

(B) I applied a commercial ELISA kit for immunoanalytical detection of the herbicide atrazine.

I verified the applicability of the ELISA system in environmental samples. I optimized the sample preparation process of soil samples for ELISA tests, and found methanol as an optimal solvent. Using the ELISA kit, I studied the decomposition of atrazine in water and soil, and found that in water at room temperature a rapid initial

decomposition rate (the active ingredient level of 1 μg/ml decreased to one-fifth within 12 days) does not decrease further resulting in a persistent residue level. In soil the 1 μg/g initial dose remains persistent, both in sand and black (chernoziom) soils, at a level of 0.35 μg/g. The study has verified that atrazine is a persistent contaminant both in water and soil.

I studied detectable atrazine levels in surface water and field soil samples collected from areas of intensive agricultural use (Békés county) and natural recreation areas (Fejér county). I found that the atrazine level is 0.31–0.40 ng/ml in water samples from agricultural areas, and 0,08-0,30 ng/ml from natural recreation areas. I demonstrated that alarmingly high atrazine contents remain in experimentally treated field soil samples one year after application (31–64% depending on application doses), and residues of atrazine application from previous years was detectable in all agricultural soil samples.

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CHARACTERIZATION OF PLANT OILS BASED ON THEIR TRIACYLGLYCEROL CONTENT BY HPLC/APCI-MS AND MALDI–TOFMS

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The main triacylglycerol compositions of fourteen different types of oil (almond, avocado, corn germ, grape seed, linseed, mustard seed, olive, peanut, pumpkin seed, sesame seed, soybean, sunflower, walnut and wheat germ) were characterized by using two different mass spectrometric techniques: high-performance liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (HPLC/APCI–MS) and matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI–TOFMS). Successful classification of the plant oils was obtained by linear discriminant analysis (LDA) based on their triacylglycerol composition. LDA resulted, that most of the samples (93.15%) were correctly classified in both cases. Among the different types of oils almond, avocado, grape seed, linseed, mustard seed, olive, sesame seed and soybean oil varieties were 100% correctly classified based on both the HPLC/APCI–MS and the MALDI–TOFMS data.

In order to reduce the analysis time a reversed-phase monolithic silica column was successfully applied using an adequate gradient elution programme at 5 $mL \cdot min^{-1}$ flow rate within 10-min run time. The reproducibility of both the retention times and peak areas were good.

Quantitation of the exact ratio of the 1,3-dilinoleoyl-2-oleoyl glycerol (LOL) and 1(3),2-dilinoleoyl-3(1)-oleoyl glycerol (LLO) isomers in grape seed, olive, pumpkin seed, soybean, sunflower and wheat germ oils was performed by using HPLC/APCI-MS in selected ion monitoring (SIM) mode. The calculated dilinoleoyl-oleoyl glycerol ratios were found to be constant values per oil varieties. The relative LOL content in grape seed, sunflower, pumpkin seed, soybean and wheat germ oils accounted for $44.2 \pm 2.6\%$, $26.8 \pm 3.2\%$, $16.7 \pm 4.6\%$, $15.9 \pm 2.9\%$ and $13.9 \pm 4.3\%$, respectively. Olive oils contained practically 100% of LLO isomer. These results indicate that the unsaturated fatty acids such as linoleic and oleic acids have ‘non-random’ distribution pattern in various oils creating the future possibility for the identification of different oils based on the LOL and LLO isomer ratio.

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PREDICTION OF PHARMACOKINETIC PARAMETERS BY COMPUTATIONAL METHODS

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A virtual high throughput screening test for the identification of potentially CNS active drugs has been developed. Discrimination was based on the knowledge available in databases containing CNS active (Cipsline from Prous Science) and inactive compounds (Chemical Directory from Sigma Aldrich). Molecular structures were represented using 2D Unity fingerprints and a feedforward neural network was trained to classify molecules regarding their CNS activity. The neural net recognizes at least 89% of CNS active compounds, what suggests to use this methodology in our virtual screening protocol.

An *in silico* screening tool for potentially CNS active compounds has been developed based on the correlation of solvation free energies and blood-brain partitioning (logBB) data available from experimental sources. Utilizing a thermodynamic approach solvation free energies were calculated by the fast and efficient GB/SA continuum solvation model which enabled us to evaluate more than 10 compounds/min. A virtual high throughput screening test for the identification of potential CP450 3A4 inhibitors has been developed. Molecular structures of inhibitors and non-inhibitors available in the Genetest database were represented using 2D Unity fingerprints and a feedforward neural network was trained to classify molecules regarding their inhibitory activity. Validation tests revealed that our neural net recognizes at least 89% of 3A4 inhibitors. Using this methodology in our virtual screening protocol METAPRINT, a metabolic fingerprint has been developed by predicting metabolic pathways and corresponding potential metabolites. Calculated drug-likeness parameters (log P and MW) were incorporated into METAPRINT to allow the encoding of metabolic diversity within a chemical library. The application of METAPRINT in the design of cassette dosing experiments was demonstrated using a library of a-1a antagonists synthesized at Glaxo Wellcome. Results obtained by Ward's clustering algorithm suggest that METAPRINTs are able to discriminate between low- and high-clearance compounds. Cassette design was performed by maximizing the intra-cassette Euclidean distances between compounds in METAPRINT space, using Monte Carlo simulated annealing approach. Calculated distances in METAPRINT space were in accordance with experimental data.

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NEW REARRANGEMENTS OF AROMATIC HYDROXYCOMPOUNDS

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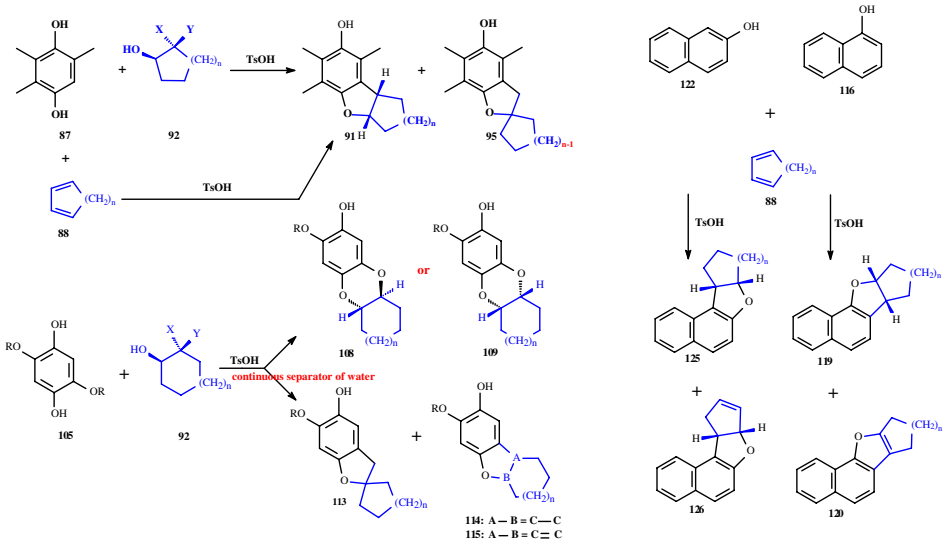
Many research groups of the world produced new, selective 5-lipoxygenase enzyme inhibitors in the last years. One of them operates in the Budapest University of Technology and Economics, Institute for Organic Chemistry led by Prof. Lajos Novák. This group had prepared a series of 5-lipoxygenase inhibitors. The most important step in the formation of these compounds was the [1,3]- or [3,3]-sigmatropic rearrangement. In my PhD work, I wanted to explore the scope and generality of these sigmatropic rearrangements and prepare novel inhibitors of 5-lipoxygenase enzyme.

I studied acid-catalyzed reactions of hidroquinone derivatives with cycloalka-1,3-dienes together with cycloalka-1,2-diols. I also studied *p*-toluenesulfonic acid-catalysed reactions of naphtols and cycloalkane-1,3-dienes. We prepared new tricyclic compounds and proposed a mechanism for these new reactions.



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POLYMER NANOCOMPOSITES; PREPARATION, STRUCTURE AND PROPERTIES

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Layered silicate nanocomposites were prepared and their structure and properties investigated in this work. Polypropylene, poly(vinyl-chloride) and polyamide were used as matrix and montmorillonite as the reinforcing component. The silicate was organophilized by various surfactants in different extents and the non-treated filler was used as reference material throughout the experiments.

In the study we verified the nucleating effect of layered silicates in polypropylene. This effect was published already, but we were the first to associate the nucleating ability of the filler with its structure. With the thorough analysis of WAXS patterns and comparison to literature data we proved that only the completely collapsed layers of the silicate nucleate PP. This explains the fact that the nucleating effect decreases or completely ceases as an effect of organophilization. We proved that the gallery structure of organophilized montmorillonite is complicated, the silicate may contain several populations of gallery distances. Gallery structure influences the extent of exfoliation and the morphology of the nanocomposite produced. Gallery structure depends on the charge density of the silicate and on the chemical structure of the surfactant used for organophilization. We found that exfoliation requires a minimum gallery distance, layers can be exfoliated by shear only if at least two linear aliphatic chains stacked on each other are located between them. We prepared and studied unplasticized PVC nanocomposites the first time in the world. We observed that the type and amount of surfactant used for organophilization considerably influences the stability of PVC, the structure of the nanocomposite and its properties. Based on the transparency of PVC composites, we proposed a simple method for the estimation of the extent of exfoliation. In this way we could show that OMMT exfoliated almost completely under the conditions used in the study. The extent of exfoliation way correlated well with parameters determined from WAXS patterns characterizing silicate and composite structure. We studied the effect of composition on nanocomposite properties in a significantly wider range than usually reported in literature. Results obtained on nanocomposites with the three matrices (PP, PVC, PA) indicated that the exfoliation of the silicate is practically never complete. The structure of the nanocomposites is heterogeneous and the distribution of the silicate layers is inhomogeneous. The complex evaluation of all results collected in the study proved that a high degree of exfoliation does not necessarily leads to nanocomposites with excellent or required properties. Composite properties depend strongly on interfacial interactions. Strong interaction may lead to stiff and brittle composites, while weak interaction results in low strength and relatively high deformability. Weak interactions are especially impor-

tant for injection molded parts with weld lines, which may become so weak that the product cannot be used at all.

Based on our technology, a pilot plant experiment was carried out in the industrial polymerization reactor of Zoltek Rt. in Nyergesújfalu between May 13 and 19, 2003. During the experiment four polyamide 6 nanocomposites were produced with different compositions. The characterization of the products is under way. If the materials pass quality control and the market accepts the new product, large-scale industrial production may start any time.

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DETECTION OF THE X- AND Y-CHROMOSOMES OF DIFFERENT BOVINAE SPECIES BY FLUORESCENCE IN SITU HYBRIDIZATION IN THE CONTEXT OF THEIR EVOLUTION AND SEPARATION OF X- AND Y-BEARING SPERMATOZOA

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Being able to preselect the sex of offspring at the time of conception ranks among the most sought-after reproductive technologies of all time. This ability runs counter the trends of nature but carries great economical improtance in today's animal breeding scheme, especially in cattle. Numerous attempts were made to develop different methods achieving this goal, mainly by the separation of X- and Y-chromosome bearing spermatozoa. One of the main components which determines the success of such a method is the way how the efficiency of the separation can be verified. The widespread use of chromosome specific DNA probes in fluorescence in situ hybridization (FISH) from the early 90's provides a fast, sensitive and statistically valid method of testing.

I adapted a simple but efficient FISH procedure using a cattle Y-chromosome fragment, specific for the BC1.2 locus. The optimization of the probe-preparing polymerase chain reaction provides the possibility of the amplification and labeling of the probe in a single step without the need of further purification. The hybridization conditions and detection methods were also optimized and the technique was used to detect the cattle Y-chromosome on metaphase chromosomes and spermatozoa. This method was also applied on yak and water buffalo specimens. Commercial probe set for labelling both cattle sex-chromosomes was not available until 2002. This probe set was applied for sexing water buffalo spermatozoa. In the case of this species, the use of sexed semen would represent an exceptional tool in some countries, like Italy, since the almost exclusive usage of buffaloes is milk and cheese production. Apart from the fact that these investigations represent the first application of FISH for sexing yak and water buffalo spermatozoa, the detection of the probes on metaphase chromosomes provides insight into the evolutionary changes and conservation of the sex-chromosomes of these Bovinae species.

Recently, the only successful method for effective separation of X- and Y-bearing spermatozoa is flow-cytometry and sorting. Although numerous healthy animals have been born using this technique, the risk of cytotoxic and/or mutagenic effects can not be ruled out completely. I developed a method for the complex and simultaneous evaluation of viability and sex of bovine spermatozoa. The method consisted of sequential steps of viability and acrosome staining and FISH detection of X- and Y-chromosomes. Owing to the specific decondensation of live cells, heads of live spermatozoa can be easily distinguished from dead ones and the X:Y ratio of live spermatozoa can be analysed simultaneously using fluorescence microscopy.

Due to the unknown, possible harmful effects of flow-cytometry the search for alternative methods is still necessary. One candidate can be the separation based on

head size differences between the two types of spermatozoa. Numerous experiments to measure this difference were made in the last 50 years, but the existence of it is still questionable. To measure the head surface area of bull spermatozoa, I carried out an experiment consisting of consecutive steps of viability and acrosome staining and fluorescent in situ hybridization investigation of the sex-chromosomes. The same cells were relocated on the digital images recorded after each step, they were classified according to morphology and membrane integrity, head areas were measured, and the corresponding sex-chromosome content was assigned. I found no significant difference between the X- and Y-chromosome bearing viable, acrosome-intact spermatozoa within bulls, however, viable cells with intact acrosome were significantly smaller than the dead, acrosome-damaged cells in the case of all bulls.

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ENANTIOSELECTIVE HETEROGENEOUS CATALYTIC HYDROGENATIONS

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The asymmetric effect of pyrrolidine methanol derivatives and (*S*)-proline esters and amides was investigated in the hydrogenation of C = C bond of isophorone and C = O bond of ethyl pyruvate. The common features of the used synthetic chiral compounds were the basic amine function in a rigid chiral environment and an aromatic ring system. It can be assumed that the basic secondary nitrogen atom is responsible for interaction with the reactant, while the aromatic ring might be the anchoring part.

Among the pyrrolidine methanol derivatives the (*S*)-α, α-diphenyl-2-pyrrolidinemethanol (DPPM) gave the best e.e. value: 42% for isophorone and 25% for ethyl pyruvate. It was supposed that the modifier *(S)*-α,α-dinaphthyl-2-pyrrolidinemethanol (DNPM) with two naphtyl groups had stronger anchoring effect, but it gave lower optical purity. We think that the two naphtyl groups on the same carbon atom make the molecule too bulky, weakens the interaction of the modifier with the catalyst surface. The (2*S*)-2(diphenylmethyl)pyrrolidine (DPMP) gave lower optical purity. As the only difference between the structures of DPPM and DPMP is the hydroxyl group, the absence of this group should be responsible for lower e.e., and it, besides *N*, probably helps the interaction with the substrate.

The designed and synthesized chiral molecules induced an e.e. in the hydrogenation of isophorone (e.e. 4–23%) and ethyl pyruvate (e.e. 4–5%). In the hydrogenation of ethyl pyruvate the e.e. values were low, corresponding to our expectations, and the (*S*)-proline as additive in the same reaction gave low optical purity, too.

However, the e.e. values obtained in the presence of novel chiral modifiers are moderate ($< 50\%$), these compounds increase the narrow choice of chiral molecules that could be used as modifiers. Furthermore the new findings improve our knowledge about the structural parts needed for asymmetric induction and how to design the appropriate chiral modifiers for heterogeneous hydrogenation. These findings represent steps in the right direction to understand the enantiodifferentiation. It is also useful to produce enantioenriched compounds, because the resolution of them is easier than that of the racemates.

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VIBRATIONAL AND QUANTUM CHEMICAL INVESTIGATION OF WEAK INTERACTIONS

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In this thesis a systematic study of the structural, vibrational and bond characteristics of various hydrogen bonded systems is presented. The characteristics of intra- and intermolecular, strong and weak hydrogen bonds and van der Waals interactions have been determined investigating over 30 molecules.

The intramolecular hydrogen bonding interaction of OH with various proton acceptor groups (C=N, NO_2, C=O, P=O, F, CF_3) in benzene derivatives have been analysed on the basis of spectroscopic and quantum chemical results. The most important properties, as the hydrogen bonding energy, the characteristic geometrical changes in the interacting groups and in the benzene rings, and the vibrational properties of intramolecular hydrogen bonding have been determined.

The structure, tautomerism, conformational properties and molecular vibrations of 4-acetyl-3(5)-amino-5(3)-methylpyrazole have been determined using quantum chemical calculations and vibrational spectroscopy. The 5-amino-3-methyl tautomer is more stable than the 3-amino-5-methyl form, however, the difference is only 2 kJ/mol at the B3LYP/6-311++G** level of theory. The hydrogen bonding has a stabilization effect on the tautomeric equilibrium and strengthens the conjugation of the NH_2 and C=O groups with the pyrazole ring.

The conformational space of the dimethylglyoxime was elucidated by density functional theory calculations determining the most stable structures. In spite of the possible intramolecular hydrogen bonding interaction in several syn conformers, the global minimum on the potential energy hypersurface is the anti/trans conformer, found previously in the crystal. The conformation of the molecule is determined by three important interactions, viz. by steric and conjugation effects as well as in a few structures by $N(O) \cdots H$ intramolecular hydrogen bonding. The vibrational analysis of dimethylglyoxime was performed utilizing a scaled computed B3LYP/6-31G* force field. With the help of this technique the vibrational spectra of this compound have been assigned.

The molecular vibrations of the bis(dimethylglyoximato)nickel(II) complex have been determined using FT-IR and FT-Raman spectroscopy and scaled quantum mechanical analysis. The initial harmonic force field was evaluated at the B3LYP/6-311++G** theoretical level and was scaled using scale factors optimized for this level. Based on the present scaled quantum mechanical force field 45 of 87 fundamentals of the molecule have been assigned.

The potential energy surface of the dimers of formaldehyde derivatives $\{(CHOY)_2$, Y = H, CH_3, F, Cl, Br, I$\}$ were investigated by quantum chemical

calculations at the MP2/6-311++G** level. The computations revealed the importance of dispersion forces in the dimer formation, while only a lesser role of the weak intermolecular hydrogen bonding was found. The most characteristic geometrical property of the dimers is the shortening of the C–H bond. A natural bond orbital analysis pointed to a slight decrease in the population of the contacting σ^*_{CH} orbitals and alterations in the intramolecular charge-transfer effects as the primary reason of the C–H contraction.

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EFFECT OF TETRAMETHYLAMMONIUM HYDROXIDE ON CELLULOSE IN COMPARISON WITH SODIUM HYDROXIDE

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Cellulose as a renewable raw material has a special significance in world's sustainable development. New and valuable products can be obtained by its physical and/or chemical modification, which is mostly carried out in the presence of a swelling agent, commercially sodium hydroxide (NaOH). Using new swelling agents for activation of cellulose might open new ways for further applications. Information on the effect of quaternary ammonium hydroxides on cellulose was very limited at the beginning of the research.

Effect of tetramethylammonium hydroxide (TMAH) on the supermolecular structure and morphology of cellulose was investigated in comparison with sodium hydroxide. Research on some physico-chemical properties of aqueous solutions (surface tension, density, viscosity, and conductivity) of both chemicals and some possible industrial applications (delignification of hemp, scouring of cotton, mercerisation) were carried out as well.

Cotton cellulose was swollen in aqueous solutions of both chemicals in equilibrium. Concentration dependence of cellulose/swelling agent interaction (heat of immersion, adsorption isotherms, retention of swelling solutions, pyrolysis) and some physico-chemical properties of swollen cellulose [degradation during swelling (degree of polymerisation), Cellulose I–Cellulose II transition (X-ray), intermolecular hydrogen bonds (FTIR), segment movement (crosslinking during γ-irradiation), accessibility (sorption capacity, heat of immersion, water retention values), light and electron microscope pictures, fibre diameter, convolution of fibre, shrinkage, breaking strength, elongation] were studied.

Tetramethylammonium hydroxide proved to be a more effective swelling and purification agent of cellulose than NaOH. This can be explained by the large size, dual (polar-apolar) character, and large activity coefficient of tetramethylammonium cation. Results can effectively be used in further studies for special modification of native cellulose.

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QUALITY MANAGEMENT TOOLS OF CHEMICAL AND BIO INDUSTRIAL DATA SYSTEMS AND PROCEDURES

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Usage of quality assurance methods in connection with databases is vital in cases when the data stored in the database are the result of measurements, and the application of the database occurs in fields representing potential danger to life or risks of financial nature. A typical case for potential danger to life is in connection with the database of explosive substances. On the other hand an inadequately implemented market research study for instance can have great financial consequences.

My PhD work included data visualization for quality assurance purposes. For this section of my research I had the opportunity to work with the database of flammable and explosive substances maintained by BAM (Bundesanstalt für Materialforschung- und prüfung) institute located in Berlin. To get hands on experiences in the field I took part in laboratory measurements performed with prEN1839T tube method equipment. I made extensions to the visualization software TRIANGLE, which is in use for data acquisition and quality control purposes at the institute. In the next phase of the work I modified the Trigon software, a program we created for 3D surface visualization at our department at the Technical University of Budapest, to produce 3D explosion range surface diagrams based on the same data.

The original TRIANGLE program had been designed by BAM staff as an aid for data input in the CHEMSAFE® database. I enhanced this program within my PhD work with parts in connection with visualization and database quality assurance. I added the stoichiometric concentration calculation and visualization, which also serve as quality assurance checks in the program. There were many curve fitting problems in the original version of the TRIANGLE software, the identification and solution of these were also part of my PhD work.

In addition to the above enhancements in the TRIANGLE program, there was a demand for a handbook to be compiled based on CHEMSAFE® explosion range data. I added to the program a script-based automation unit, which would sequentially access several datasets and, with the use of template files, inserts information from them in an editable and printable document. This task involved further program modifications including the improvement of the triangular and Cartesian charts.

With the implementation of the automatic processing, it also became possible to perform quality analysis on large number of datasets. Utilizing this new feature I implemented a testing technique for analyzing the quality of substituted missing turning points with respect to different extrapolation and curve fitting methods. I modified a real, complete data set, by eliminating one, then two more points at the turning point of the curve. I examined the effects of the extrapolation on the

characteristic values calculated for the explosion ranges, and compared the results of the different methods.

During the implementation of the curve fitting algorithms for the explosion range datasets came the idea to plot explosion surfaces when several sets of measurements were available for the same gas components at different starting temperatures or starting pressures. Tool for this was the Trigon program, which had been developed at the Department of Chemical Engineering under my supervision. With some modifications, this program could be made capable to visualize any ternary systems. During my PhD work, I adapted this program for the visualization of vapor liquid equilibrium data, after then for explosion limit surfaces of ternary gas systems. In case of the latter, I implemented a new interpolation method for the surface section near the turning line.

The Trigon program can be controlled by three means: using a Turbo Vision user interface (character based windows/menu/mouse control), command line control, and control by external programs (such as web server side applications). The web-server controlled execution makes it possible for distant users to remotely use the program. Remote-controlled programs offer several advantages, of which only some are utilized in this particular application, thus the significance of this development is mainly theoretical.

In every area of my PhD work I had to produce documentation that was adequate even for industrial applications. To meet an industrial sector's particular demands, I had to take into account the corresponding quality assurance and quality control standards in their complex arrangement and practice. The chemical and bio industrial databases can be created not just by experimental measurements, as part of my PhD work I designed a generally applicable information processing method for market research as a tool for data acquisition in food industrial applications.

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